A Longitudinal Study of Chronic Lead Exposure and Physical Growth in Boston Children

Rokho Kim,[1,2,3] Howard Hu,[1,3] Andrea Rotnitzky,[4] David Bellinger,[5] and Herbert Needleman[6]

[1]Department of Environmental Health and [2]Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115 USA; [3]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115 USA; [4]Department of Biostatistics, Harvard School of Public Health, Boston, MA 02115 USA; [5]Department of Neurology and Mental Retardation Research Center, Children's Hospital, Harvard Medical School, Boston, MA 02115 USA; [6]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA

We investigated the cross-sectional and longitudinal relationships between chronic exposure to lead and physical growth among a cohort of children reassessed 13 years after initial examination. We measured weight, height, and dentin lead levels of 270 children in 1975–78. In 1989–1990 we reexamined 79 of these children for measurement of weight, height, and bone lead levels by means of *in vivo* K X-ray fluorescence. To avoid potential confounding by race and chelation history, analysis was restricted to white subjects without a history of lead chelation therapy. A total of 236 subjects provided complete information for the study of cross-sectional relationship between dentin lead levels and physical growth: 58 subjects for the study of longitudinal relationship between dentin lead levels and changes in physical growth and 54 subjects for the study of longitudinal relationship between bone lead levels and changes in physical growth. Dentin lead levels averaged 14.9 μg/g; tibia and patella lead levels averaged 1.2 and 5.0 μg/g, respectively. With control for potential confounders including age, sex, baseline body size, and mother's socioeconomic status, $\log_{10}$ dentin lead level was positively associated with body mass index as of 1975–1978 (ß = 1.02, $p = 0.03$) and increase in body mass index between 1975–78 and 1989–90 (ß = 2.65, $p = 0.03$). Bone lead levels were not significantly associated with physical growth. This is the first study relating chronic lead exposure to body mass index. The results suggest that chronic lead exposure in childhood may result in obesity that persists into adulthood. *Key words*: body mass index, bone lead, growth, lead toxicity, tooth lead. *Environ Health Perspect* 103:952–957 (1995)

Although the adverse effect of overt plumbism on physical growth has long been recognized (*1,2*), the effect of low-level lead exposure on physical growth was first explored by Schwartz et al. using data from the National Health and Nutrition Examination Survey (NHANES) II of 1976–1980 (*3*). The NHANES II data for 2695 children 7 years old indicated that blood lead level (range = 4–35 μg/dl) was a statistically significant predictor of children's height, weight, and chest circumference, with control for age, race, sex, and nutritional covariates. However, the cross-sectional nature of the NHANES II survey limited causal inference regarding the relationship.

The results of subsequent studies have been inconsistent. A retrospective study of the growth of 54 children from birth to 48 months of age suggested a negative correlation between weight gain and higher blood lead between 15 and 24 months of age (*4*). Two longitudinal studies did not find any significant association between blood lead and physical growth (*5,6*). In another longitudinal study, covariate-adjusted heights at 15 and 33 months of age were negatively associated with postnatal blood lead concentrations (*7,8*).

Considering that physical growth is a time-integrated outcome, use of biomarkers of chronic exposure such as tooth lead and bone lead might be more advantageous than blood lead in investigating the association. Blood lead reflects relatively recent exposure over a few months, and the biological half-life of lead in children was several times shorter than that for adults (*9,10*). Indeed, with control for other variables, including the child's medical history, dietary history, behavior, tobacco smoking of parents, and sociodemographic factors, a study of Danish children showed an inverse association between tooth lead and height (*11*).

Lead concentrates in mineralized tissue such as bone and teeth. The concentration of lead in the circumpulpal dentin of deciduous teeth has been a useful biomarker of cumulative lead exposure in studies of the chronic toxicity of lead (*12*). It provides more valid information than does tooth enamel on systemic absorption of environmental lead into the body over several years prior to shedding (*13–16*).

Bone accumulates lead throughout life, eventually serving as the repository for 95% of an individual's lead burden (*17*). Because of the long half-life of lead in bone, bone lead provides an index of cumulative exposure over decades. Direct measurement of lead in bone by means of an *in vivo* X-ray fluorescence (XRF) technique has been developed as a promising biomarker during the last decade (*18,19*). On the basis of the electron orbit where it provokes the emission of fluorescent photons from lead atoms, the XRF technique is classified into L-line XRF (L-XRF) and K-line XRF (K-XRF).

The K-XRF technique is relatively stable and reliable. Its accuracy is not affected by overlying skin thickness or movement, and it permits measurement of lead levels in bone cortex and marrow tissues deeper than L-XRF (*20,21*). It is noninvasive, involves low-level radiation dose (less than 2.5% of the effective dose of a chest X-ray examination in adults), and takes 15–30 min to measure one bone site (longer time renders better precision) (*20,22*).

To our knowledge, no studies examining the effect of chronic lead exposure on body mass index (weight in kilograms divided by the square of the height in meters; BMI) have been previously reported, although BMI, as an index of obesity, has long been shown to be an important risk factor for hypertension, diabetes, and coronary heart disease (*23,24*). We investigated the effect of chronic lead exposure on BMI as well as on weight and height in a cohort that was examined at a 13-year interval. We explored the cross-sectional relationship between dentin lead level and physical growth in each examination of the cohort, then assessed the longitudinal relationship between dentin lead level in child-

Address correspondence to R. Kim, Occupational Health Program, Harvard School of Public Health, 665 Huntington Avenue, Boston MA 02115 USA.
This study was supported by NIEHS grant ES04095, NIEHS Occupational and Environmental Health Center grant 2P30 ES00002, NIEHS ES 05257-01A1, and NIH grant NCRR GCRC M01 RR02635. R.K. was supported by a training grant award from NIEHS Basic Superfund P42-ES05947 and a scholarship from the Department of Labor of the Republic of Korea. The K-XRF instrument used in this work was developed by ABIOMED, Inc. of Danvers, Massachusetts, with support from NIH SBIR 2R44 ES03918-02. Many thanks to Doug Burger for his technical assistance with the instrument and Joel Schwartz for valuable comments on the study findings.
Received 12 April 1995; accepted 22 June 1995.

hood and physical growth from childhood through early adulthood. The study protocol was approved by the institutional review boards of Children's Hospital (Boston) and Brigham and Women's Hospital, and informed consent was obtained from all participants in the study.

Methods

Subjects. The initial sample was chosen from a population of 3329 first and second graders in Chelsea and Somerville, Massachusetts, between 1975 and 1978. From this group, 270 English-speaking children with initial dentin lead levels >24 ppm (upper 10th percentile) or <8.7 ppm (lower 10th percentile) were recruited for a study of neurobehavioral effects of lead. Methods used to define eligible subjects are described in detail elsewhere (*25*).

In 1988, 132 members (mean age, 18.4 years) of this cohort were recruited to participate in a follow-up evaluation of their neuropsychological performance. Of these, 79 subjects (60% of the base population) participated in the additional follow-up in 1989 and 1990. Among those who did not, 5 (3.8%) refused, 34 (25.8%) could not be located, 8 (6.0%) agreed to participate contingent on a return visit to Boston during the data collection period, 5 (3.8%) agreed to participate but repeatedly failed to keep appointments, and 1 withdrew consent during the study.

To control for confounding by race, we restricted the study to white subjects (N = 251 as of 1975–1978). Growth velocity has been known to significantly increase after calcium disodium ethylenediamine tetraacetic acid (EDTA) chelation therapy in lead-poisoned children aged 2–5 years (*26*). Subjects with high dentin lead levels were more likely to have undergone chelation therapy in childhood than those with low levels. Following chelation, subjects might have lower internal doses of lead than expected on the basis of their dentin lead levels. Six subjects had a history of chelation. To eliminate potential confounding by chelation therapy, the principal analyses were restricted to nonchelated subjects. However, results from analyses including the chelated subjects are also presented.

Physical growth. Subjects' weight and height were measured (in light clothes and barefoot) to the nearest quarter pound and quarter inch, respectively, with use of a Health O Meter (Continental Scale Corp., Bridgeview, Illinois) at the initial interview in 1975–1978 and during the examination in 1989–1990.

Tooth lead measurement. Shed deciduous teeth donated by subjects were cleansed ultrasonically, and those with fillings were discarded from consideration. The specimens were then mounted in lead-free wax on the cutting stage of a Buehler low-speed saw (Buehler Ltd., Lake Bluff, Illinois). A 1-mm slice was taken from the central sagittal plane of each tooth at a single pass. The central slice was then placed on an anvil and split with a small chisel along a line from the pulp canal to the dentin–enamel junction. The larger portions of the slices, along with the residual adjacent segments, were filed in numbered pill boxes for later confirmatory analysis. The smaller portion, composed primarily of dentin, was then analyzed for lead by means of anodic stripping voltammetry, as described elsewhere (*27*). If three dentin lead values were available, two concordant values were required; if four values were available, three concordant values were required. We used the mean of all available dentin lead values for a child as the exposure index.

Bone lead measurement. We measured bone lead in the tibia and patella of each patient using our prototype K-XRF instrument (ABIOMED, Inc., Danvers, MA). The physical principles, technical specifications, and validity of K-XRF instruments are described in detail elsewhere (*28–30*). In short, this instrument uses a ^{109}Cd γ-ray source to provoke the emission of fluorescent photons from target tissue that are detected, counted, and arrayed on a spectrum. The net lead signal is determined after subtraction of background counts by means of a linear least-squares algorithm. The lead fluorescence signal is then normalized to the elastic or coherently scattered X-ray signal, which arises predominantly from the calcium and phosphorus present in bone mineral. The unit of measurement is microgram of lead per gram of bone mineral.

Because the instrument provides a continuous, unbiased point estimate that oscillates around the true bone lead value, negative point estimates are sometimes produced when the true bone lead value is close to zero. The instrument also provides an estimate of uncertainty associated with each measurement, which is derived from a goodness of fit calculation of the spectrum curves and is equivalent to a single standard deviation. Although a minimum detectable limit calculation of twice this value has been proposed for interpreting a bone lead estimate for an individual (*31*), use of all point estimates makes better use of the data for a population in epidemiologic studies (*32,33*). Recently, we have specifically addressed the methodological issues of using negative values and values below the conceptual limit of detection in epidemiologic studies (*33*). Our experiment indicated that retaining all values of bone lead concentration provides less bias and greater efficiency in comparing the mean or median levels of bone lead of different populations.

Measurements were taken at the midshaft of the left tibia and at the left patella after each region had been washed with a 50% solution of isopropyl alcohol. The K-XRF beam collimator was seated perpendicular to the bone surface for the tibia and at 30° in the lateral direction for the patella.

Covariates. Information on potential confounding variables and effect modifiers was obtained from data collected by questionnaire and examination in 1975–1978. Age, sex, race, birth weight, mother's socioeconomic status (dichotomized by Hollingshead class I–III versus IV–V), medical history of chelation therapy for lead poisoning as of 1975–1978, and age at the time of K-XRF measurement in 1989–1990 were selected *a priori* as potential covariates.

Statistical analysis. The main purpose of the analysis was to relate physical growth (dependent variables) to lead biomarkers (independent variables) with control for potential covariates. Before the main analysis, extreme outliers in values of height, weight, and BMI were detected by the generalized extreme studentized deviate (ESD) many-outlier procedure, with a Bonferroni-corrected level (*34*). Lowess smoothing plots between covariate-adjusted dependent variables and covariate-adjusted independent variables were used to evaluate the form of the dose–response relationship and to suggest appropriate transformations of variables (*35*).

Three sets of multiple linear regression models were fitted (Fig. 1). First, to determine whether dentin lead level was cross-sectionally associated with physical growth in childhood (1975–1978), regressions of dentin lead on each physical outcome were carried out, with control for age, sex, birth weight, and mother's socioeconomic status (model 1). Second, to determine whether the dentin lead level was prospectively associated with changes in physical growth between 7 and 20 years of age, regressions of dentin lead on each physical outcome were carried out, with control for age increase, age as of 1975–1978, sex, mother's socioeconomic status, and physical growth as of 1975–1978 (model 2). Finally, to determine whether bone lead levels around the age of 20 years were retrospectively associated with changes in physical growth between 7 and 20 years of age, regressions of bone lead levels (i.e., tibia lead levels, patella lead levels, or mean bone lead levels) on each physical outcome were carried out, with control for age increase,

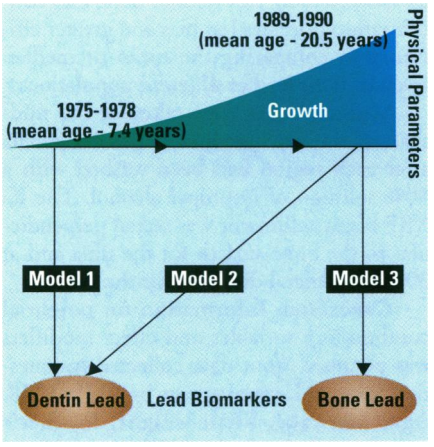

Figure 1. Longitudinal structure of the data and the statistical models in the study of the effect of lead exposure on physical growth. The dependent variable of model 1 is physical parameter [weight, height, or body mass index (BMI)] as of 1975–78. Independent variables of model 1 are $\log_{10}$ dentin lead level, age, sex, birth weight, and mother's socioeconomic status as of 1975–78. For models 2 and 3, the dependent variable is physical parameter (weight, height, or BMI) change between 1975–78 and 1989–90. The independent variable of interest is $\log_{10}$ dentin lead level as of 1975–78 for model 2 and bone lead (tibia, patella, or mean bone lead) level for model 3. Other independent variables adjusted in models 2 and 3 are age as of 1975–78, age increase between 1975–78 and 1989–90, sex, mother's socioeconomic status as of 1975–78, and physical parameter (weight, height, or BMI, respectively)

age as of 1975–1978, sex, mother's socioeconomic status, and physical growth as of 1975–1978 (model 3-1 for tibia lead levels, model 3-2 for patella lead levels, and model 3-3 for mean bone lead levels).

Results

A total of 237 white subjects without a history of chelation had complete information for fitting model 1. An extreme outlier at level <0.0002 (0.05/237) for BMI as of 1975–1978 was detected by the ESD procedure. This extremely obese child (weight 49.2 kg, height 1.27 m, and BMI 30.5 kg/m^2 at the age of 7.1 years) was excluded from subsequent analyses. The remaining 236 subjects used in fitting model 1 did not significantly differ from the remaining nonchelated subjects in dentin lead, weight, height, BMI, sex, birth weight, or mother's socioeconomic status (Table 1).

Of the 79 participants in the last examination, 60 nonchelated white subjects had complete information for fitting model 2, which requires physical parameter variables measured at both the 1975–1978 and the 1989–1990 examinations. The ESD procedure detected two extreme outliers at level <0.0008 (0.05/61) for BMI change between 1975–1978 and 1989–1990. One outlier, with a BMI increase of 23.2 kg/m^2, had a weight of 102.2 kg, a height of 1.60 m, and a BMI of 39.9 kg/m^2 at the age of 19.8 years. The other outlier, with a BMI increase of 20.7 kg/m^2, had a weight of 112.1 kg, a height of 1.68 m, and a BMI of 39.9 kg/m^2 at the age of 21.2 years.

The 58 study subjects used in fitting model 2 did not significantly differ from the remaining nonchelated subjects in dentin lead, physical growth as of 1975–1978, sex, and birth weight. However, mother's socioeconomic status as of 1975–1978 for these subjects was higher (p<0.01 by Fisher's exact test). Out of these 58, 4 subjects did not undergo bone lead measurements, resulting in 54 subjects for model 3. They did not significantly differ from the remaining nonchelated subjects in dentin lead, physical growth as of 1975–1978, sex, or birth weight, but mother's socioeconomic status did differ.

At the time of the 1975–1978 examination, weight, height, and BMI averaged 26.1 kg (SD = 5.1, range = 17.5–45.4), 1.26 m (SD = 0.06, range = 1.09–1.49), and 16.3 kg/m^2 (SD = 2.3, range = 10.1–25.7), respectively. Dentin lead levels averaged 14.9 (SD = 11.5, range = 2.8–66.3). At the time of the 1989–1990 examination, weight, height, and BMI averaged 69.7 kg (SD = 15.5, range = (49.9–116.7), 1.71 m (SD = 0.10, range = 1.55–1.91), and 23.65 kg/m^2 (SD = 3.54, range = 18.09–33.03),

Table 1. Characteristics of subjects included in and excluded from analyses of lead and physical growth[a]

	Model 1: subjects in 1975–78 study (N = 270)			Model 2: nonchelated subjects, 1989–90 study (N = 76)	
Characteristic	Analyzed (N = 236)	Nonchelated, excluded (N = 28)[b]	Chelated, excluded (N = 6)	Analyzed (N = 58)	Excluded (N = 18)[b]
Age, 1975–78 (years)	7.4±0.6 (5.9–9.0)	7.4±0.6 (6.5–9)	7.3±0.9 (6.1–8.9)	7.4±0.5 (6.1–8.8)	7.4±0.7 (6.5–8.42)
Sex (% female)	47	54	100	53	50
Birth weight (kg)	3.3±0.5 (1.0–4.7)	3.3±0.6 (2.0–4.6)	3.2±0.5 (2.7–3.8)	3.4±0.5 (2.2–4.4)	3.2±0.7 (1.0–4.3)
Mother's socioeconomic status (% high)	11	8	0	10	24
Weight, 1975–78 (kg)	26.1±5.1 (17.5–45.4)	27.0±6.0 (19.3–49.1)	20.5±2.1 (18.5–23.0)	26.3±5.3 (17.5–43.1)	26.4±3.7 (22.5–34.2)
Height, 1975–78 (m)	1.26±0.06 (1.09–1.49)	1.26±0.08 (1.02–1.44)	1.19±0.04 (1.14–1.25)	1.27±0.06 (1.13–1.42)	1.28±0.07 (1.19–1.44)
BMI, 1975–78 (kg/m^2)	16.3±2.3 (10.1–25.7)	16.9±3.7 (13.1–30.5)	14.4±1.0 (13.0–15.3)	16.22.1 (13.3–21.8)	16.2±1.4 (14.1–19.2)
Dentin lead as of 1975–78 (ppm)	14.9±11.5 (2.8–66.3)	17.0±15.9 (2.6–51.4)	35.9±15.8 (18.9–61.2)	12.9±9.8 (2.9–51.8)	13.6±11.5 (4.6–50.4)
$\log_{10}$ dentin lead, 1975–78 (ppm)	1.06±0.32 (0.44–1.82)	1.06±0.38 (0.41–1.71)	1.52±0.19 (1.28–1.79)	1.00±0.31 (0.46–1.71)	1.03±0.29 (0.66–1.70)
Age, 1989–90 (years)	NA	NA	NA	20.5±0.7 (18.7–21.8)	20.3±1.0 (18.8–21.7)
Weight, 1989–90 (kg)	NA	NA	NA	69.7±15.5 (49.9–116.7)	75.7±16.3 (59.0–112.1)
Height, 1989–90 (m)	NA	NA	NA	1.71±0.10 (1.55–1.91)	1.28±0.07 (1.19–1.44)
BMI, 1989–90 (kg/m^2)	NA	NA	NA	23.6±3.54 (18.09–33.03)	26.2±6.1 (20.4–39.9)
Weight change from 1975–78 to 1989–90 (kg)	NA	NA	NA	43.5±13.1 (23.8–80.5)	49.7±15.7 (28.8–79.2)
Height change from 1975–78 to 1989–90 (m)	NA	NA	NA	0.44±0.09 (0.18–0.58)	0.42±0.08 (0.30–0.60)
BMI change from 1975–78 to 1989–90 (kg/m^2)	NA	NA	NA	7.49±2.67 (2.83–15.87)	10.44±5.55 (4.90–23.15)
Tibia lead, 1989–90 (μg/g)[b]	NA	NA	NA	1.2±4.4 (-7–13)	2.1±6.3 (-9–19)
Patella lead, 1989–90 (μg/g)	NA	NA	NA	5.08.1 (-10–23)	5.4±9.9 (-13–25)
Mean bone lead, 1989–90 (μg/g)	NA	NA	NA	3.14.7 (-5.5–14)	3.9±4.8 (-4–12.5)

Abbreviations: NA, not applicable; BMI, body mass index.
[a]Means ± SD and ranges (in parentheses) presented where appropriate.
[b]Subjects excluded from analysis are those with incomplete information, and those of nonwhite race.

respectively. Tibia and patella lead estimates averaged 1.2 μg/g (SD = 4.4, range = -7–13), and 5.0 μg/g (SD = 8.1, range = -10–23), respectively.

In exploratory data analyses, the lowess smoothing curves of covariate-adjusted outcome variables and covariate-adjusted predictor variables were curvilinear and slightly upwardly convex. Lowess smoothing after logarithmic transformation of dentin lead levels provided a more linear fit. For the sake of interpretability of the scale, we used $\log_{10}$ dentin lead level in linear regression analyses.

With control for age as of 1975–1978, sex, birth weight, and mother's socioeconomic status, $\log_{10}$ dentin lead in nonchelated, nonoutlying subjects was significantly associated with BMI (N = 236, ß = 1.02, 95% CI, 0.12–1.93, p = 0.03; Table 2), but not with weight or with height. The inclusion of chelated subjects slightly reduced the regression coefficient for BMI of $\log_{10}$ dentin lead (N = 240, ß = 0.88, 95% CI, -0.01–1.76, p = 0.05). Additional inclusion of an extreme outlier obscured the association between BMI and $\log_{10}$ dentin lead (N = 241, ß = 0.65, 95% CI, 0.31–1.60, p = 0.19). When the same regression models were fitted to a subgroup who participated in the 1989–1990 examination and had complete information for model 2, the confidence bounds were slightly widened, which might result from reduced sample size (N = 58, ß = 1.82, 95% CI, -0.06–3.69, p = 0.06).

With control for BMI as of 1975–1978, age increase, age as of 1975–1978, sex, and mother's socioeconomic status, $\log_{10}$ dentin lead was significantly associated with BMI change between 1975–1978 and 1989–1990 among nonchelated, nonoutlying subjects (ß = 2.65, 95% CI, 0.33–4.97, p = 0.03; Table 2). The inclusion of a chelated subject did not appreciably change the regression coefficient for BMI change of $\log_{10}$ dentin lead (ß = 2.50, 95% CI, 0.27–4.74, p = 0.03). However, inclusion of the two outliers obscured the association (ß = 2.48, 95% CI, 0.79–5.75, p = 0.13). There were no significant associations between $\log_{10}$ dentin lead and weight, or between $\log_{10}$ dentin lead and height.

No significant association was observed between bone lead as of 1989–1990 and any of the changes in physical growth between 1975–1978 and 1989–1990, with control for physical growth as of 1975–1978, age increase, age as of 1975–1978, sex, and mother's socioeconomic status. The results were similar when chelated subjects and/or outliers were included.

Discussion

We observed a weak but significantly positive association between childhood dentin lead level and BMI in both cross-sectional and longitudinal analyses. A 10-fold increase in dentin lead level was associated with an increase of 1.02 kg/m^2 in BMI at the age of 7 years. A 10-fold increase in dentin lead level was also associated with an increase in BMI change of 2.65 kg/m^2 from age 7 to age 20.

The point estimates of the regression coefficient for weight and for change in weight were positive; those for height and for change in height were negative, but their interval estimates all included zero. Because increased BMI results from increased weight and/or decreased height, it may have served as a more sensitive indicator for the association between physical growth and chronic lead exposure in our study. Bone lead levels at the age of 20 years were not significantly associated with any physical growth changes between 7 and 20 years of age.

Because dentin lead level reflects chronic exposure to lead during the several years prior to the shedding of teeth, our findings suggest that children exposed to lead in early childhood experience greater BMI gain during the period between 7 and 20 years of age than those less exposed. It is possible that obese children ingested more environmental lead from tap water, canned foods, dusts, and paint chips during early childhood. This reverse causality can explain the cross-sectional association, but hardly the longitudinal association. In our longitudinal model, the exposure (the accumulation of lead in the tooth) obviously preceded the effect (the increase in BMI), thereby supporting the attribution of a causal role to lead.

Blood lead level was inversely associated with both height and weight in NHANES II data (*3*). An association of blood lead with BMI was not examined, and the index of exposure was blood lead, not dentin lead, in the NHANES II. Thus, any comparison between this study and the NHANES II study should be made carefully. Nevertheless, it may be interesting to examine whether there is also a significant association between blood lead and BMI in the NHANES II data.

On the basis of coefficients of variation for weight (approximately 20%) and for height (approximately 5%) in our data, we estimated that the cross-sectional analysis of the 1975–1978 data (N = 236) had 80% power to detect the 7% difference in mean of weight and the 1.8% difference in mean of height. Smaller effects would not be detectable with 80% power.

Reduced pituitary responsiveness to hypothalamic stimuli in terms of growth hormone releasing factor or thyrotropin-releasing hormone has been postulated as a pathophysiologic mechanism for lead's effect on physical growth. A recent neuroendocrine study showed that peak human growth hormone and insulinlike growth factor I responses to the L-dopa insulin test were low in lead-poisoned children (*26*). The authors concluded that lead-induced reduction in stature may be due to diminished human growth hormone secretion, which in turn results in reduced insulinlike growth factor I secretion, or that lead may directly inhibit insulinlike growth factor I formation. Blunted response of thyroid-stimulating hormone and growth hormone to stimulatory challenge have been observed in lead-poisoned children (*36*) as well as in rats exposed to low-level lead (*37*). It is possible that our findings reflect similar endocrine effects of low-level lead exposure.

Table 2. Partial regression coefficient of $\log_{10}$ dentin lead (ppm) in multiple linear regression of physical growth in study of the relationship between lead exposure and physical growth[a]

	Partial regression coefficient dependent variables		
Model (N)	Weight (kg)	Height (m)	BMI (kg/m^2)
1 (236)	1.340 (0.991)[b]	-0.009 (0.011)	1.023* (0.458)
2 (58)	7.118 (4.176)	-0.028 (0.025)	2.650* (1.156)
3-1 (54)	-0.038 (0.327)	-0.003 (0.002)	0.077 (0.088)
3-2 (54)	-0.187 (0.159)	-0.001 (0.001)	-0.042 (0.043)
3-3 (54)	-0.314 (0.286)	-0.003 (0.002)	-0.037 (0.078)

BMI, body mass index.

[a]Dependent variable of model 1 is weight, height, or BMI as of 1975–78. Independent variables of model 1 are $\log_{10}$ dentin lead level, age, sex, birth weight, and mother's socioeconomic status as of 1975–78. For models 2, 3–1, 3–2 and 3–3, dependent variable is change in weight, in height, or in BMI between 1975–78 and 1989–90. Independent variable of interest is $\log_{10}$ dentin lead level as of 1975–78 for model 2; tibia lead level for model 3–1, patella lead level for model 3–2, and mean bone lead level as of 1989–90 for model 3–3. Other independent variables adjusted in models 2 and 3 are age as of 1975–78, age increase between 1975–78 and 1989–90, sex, mother's socioeconomic status as of 1975–78, and physical parameter (weight, height, or BMI, respectively) as of 1975–78.

[b]Standard errors in parentheses.

*p<0.05.

The positive findings of this study may have resulted by chance. As we conducted multiple statistical tests using the same data set, the probability of a type I error may be larger than the nominal level of 0.05. Thus, further study with a larger sample size is encouraged to corroborate our findings.

A possible source of bias is our limited success in locating and enrolling members of the cohort for follow-up because of the increased migration from home that occurs around age 20. However, the characteristics of the population, including dentin lead levels, did not differ significantly between those who participated in this follow-up and those who did not. As physical growth and covariates were measured blindly with respect to the status of dentin and bone lead levels, observation bias is not likely.

We eliminated potential confounding effects of race and chelation by restricting the main analysis to white, nonchelated subjects. However, such potential confounding variables as food intake and parental body size were not controlled for in our study because this information was not available. We intended to reduce confounding effects of those variables by adjusting for mother's socioeconomic status. Still, it is possible that genetic (*38,39*) and nongenetic risk factors (*23*) for increased BMI might result in increased dentin lead levels through unknown mechanism. Further studies more thoroughly controlling for those potential confounders are awaited.

BMI is a major risk factor for elevated blood pressure (*23,24*). It has been noted that blood pressure was positively associated with blood lead levels before and after control for age, BMI, and other related factors (*40–45*). However, the association between blood lead and blood pressure is not conclusive yet (*45*), because it is very weak (1 to 2 mm Hg for every doubling in blood lead levels in middle-aged men) and influenced by the inclusion of covariates in the statistical model such as alcohol consumption and cigarette smoking (*41*).

Our finding that childhood lead exposure may predict increased BMI that persists into adulthood is suggestive of an indirect path to elevated blood pressure related to chronic lead exposure. If our finding is replicable and robust, the ramifications are significant. The previously described association between low-level lead exposure and elevated blood pressure may be stronger than currently assumed, if the effect of lead on obesity is also taken into account.

References

1. Nye LJJ. An investigation of the extraordinary incidence of chronic nephritis in young people in Queensland. Med J Aust 2:145–159 (1929).
2. Johnson NE, Tenuta K. Diets and lead blood levels of children who practice pica. Environ Res 18:369–376 (1979).
3. Schwartz J, Angle C, Pitcher H. Relationship between childhood blood lead levels and stature. Pediatrics 77:281–288 (1986).
4. Angle CR, Kunzelman DR. Increased erythrocyte protoporphyrins and blood lead—a pilot study of childhood growth patterns. J Toxicol Environ Health 26:149–156 (1989).
5. Sachs HK, Moel DI. Height and weight following lead poisoning in childhood. Am J of Disease Child 143:820–822 (1989).
6. Greene T, Ernhart CB. Prenatal and preschool age lead exposure: relationship with size. Neurotoxicol Teratol 13:417–427 (1991).
7. Shukla R, Bornschein RL, Dietrich KN, Buncher CR, Berger OG, Hammond PB, Succop PA. Fetal and infant lead exposure: effects on growth in stature. Pediatrics 84:604–612 (1989).
8. Shukla R, Dietrich KN, Bornschein RL, Buncher CR, Berger OG, Hammond PB. Lead exposure and growth in the early preschool childhood. Pediatrics 88:886–892 (1991).
9. Rabinowitz MB, Wetherill GW, Kopple JD. Lead metabolism in the normal human: stable isotope studies. Science 182:725–772 (1973).
10. Duggan MJ. The uptake and excretion of lead by young children. Arch Environ Health 38:246–247 (1983).
11. Lyngbye T, Hansen ON, Grandjean P. The influence of environmental factors on physical growth in school age: a study of low level lead exposure. In: International conference on heavy metals in the environment, vol 2 (Lindberg SE, Hutchinson TC, eds). Edinburgh, UK:CEP Consultants, Ltd., 1987;210–212.
12. Needleman HL, Gatsonis CA. Low-level lead exposure and the IQ of children: a meta-analysis of modern studies. J Am Med Assoc 263:673–678 (1990).
13. Carroll KG, Needleman HL, Tuncay OC, Shapiro IM. The distribution of lead in human deciduous teeth. Experientia 28:424–435 (1972).
14. Shapiro IM, Needleman HL, Tuncay OC. The lead content of human deciduous and permanent teeth. Environ Res 5:467–470 (1972).
15. Grandjean P, Hansen ON, Lyngbye K. Analysis of lead in circumpulpal dentin of deciduous teeth. Ann Clin Lab Sci 14:270–275 (1984).
16. Rabinowitz MB, Leviton A, Bellinger D. Relationships between serial blood lead levels and exfoliated tooth dentin lead levels: models of tooth lead kinetics. Calcif Tissue Int 53:338–341 (1993).
17. Barry PSI, Mossman DB. Lead concentration in human tissues. Br J Ind Med 27:339–351 (1970).
18. Landrigan PJ, Todd AC. Direct measurement of lead in bone—a promising biomarker. J Am Med Assoc 271:239–240 (1994).
19. Hu H, Milder FL, Burger DE. X-ray fluorescence: issues surrounding the application of a new tool for measuring burden of lead. Environ Res 49:295–317 (1989).
20. Hu H, Milder F, Burger DE. X-ray fluorescence measurements of lead burden in subjects with low-level community lead exposures. Arch Environ Health 45:335–341 (1990).
21. Todd AC, Chettle DR. *In vivo* X-ray fluorescence of lead in bone: review and current issues. Environ Health Perspect 102:172–177 (1994).
22. Chettle DR, Scott MC, Somervaille LJ. Lead in bone: sampling and quantitation using K X-rays excited by ^{109}Cd. Environ Health Perspect 91:49–55 (1991).
23. Mann GV. The influence of obesity on health. N Engl J Med 291:178–185,226–232 (1974).
24. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Rosner B, Monson RR, Speizer FE, Hennekens CH. A prospective study of obesity and risk of coronary heart disease in women. N Engl J Med 322:882–889 (1990).
25. Needleman HL, Gunnoe C, Leviton A, Reed R, Peresie H, Maher C, Barrett P. Deficits in psychologic and classroom performance of children with elevated dentine lead levels. N Engl J Med 300:689–695 (1979).
26. Huseman CA, Varma MM, Angle CR. Neuroendocrine effects of toxic and low blood lead levels in children. Pediatrics 90:186–189 (1992).
27. Needleman HL, Davidson I, Sewell EM, Shapiro IM. Subclinical lead exposures in Philadelphia schoolchildren. Identification by dentine lead analysis. N Engl J Med. 290:245–248 (1974).
28. Burger D, Morsillo P, Adams B, Hu H, Milder FL. Automated instrument for making K X-ray fluorescence measurements in human bone. Basic Life Sci 55:287–293 (1990).
29. Somervaille LJ, Chettle DR, Scott MC. In vivo measurement of lead in bone using X-ray fluorescence. Phys Med Biol 30:929–943 (1985).
30. Jones KW, Schidlovsky G, Williams FH, Wedeen RP, Batuman V. In vivo determination of tibial lead by K X-ray fluorescence with a ^{109}Cd source. In: In vivo body composition studies (Ellis KJ, Yasumura S, Morgan WD, eds). London:Institute of Physical Science in Medicine, 1987;363–373.
31. Gordon CL, Chettle DR, Webber CE. An improved instrument for the in vivo detection of lead in bone. Br J Ind Med 50:637–641 (1993).
32. Hu H, Aro A, Rotnitzky A. Bone lead measured by X-ray fluorescence: epidemiologic methods. Environ Health Perspect 103(suppl 1):105–110 (1995).
33. Kim R, Aro A, Rotnitzky A, Amarasiriwardena C, Hu H. K X-ray fluorescence measurements of bone lead concentration: the analysis of low-level data. Phys Med Biol (in press).
34. Rosner B. Percentage points for a generalized ESD many-outlier procedure. Technometrics 25:165–172 (1983).
35. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. J Am Stat Assoc 74:829–836 (1979).
36. Huseman CA, Moriarty CM, Angle CR. Childhood lead toxicity and impaired release of thyrotropin stimulating hormone. Environ Res 42:524–533 (1987).
37. Camoratto AM, White LM, Lau YS, Ware GO, Berry WD, Moriarty CM. Effect of exposure to low level lead on growth and growth hormone release in rats. Toxicol 83:101–114 (1993).
38. Seltzer CC. Genetics and obesity. In: Physiopathology of adipose tissue (Vague J,

Denton RM, eds). Amsterdam:Excerpta Medica, 1969;325–334.
39. Clark PJ. The heritability of certain anthropometric characters as ascertained from measurement of twins. Am J Hum Genet 8:49–54 (1956).
40. Pirkle JL, Schwartz J, Landis R, Harlan WR. The relationship between blood lead levels and blood pressure and its cardiovascular implications. Am J Epidemiol 121:246–258 (1985).
41. Pocock SJ, Shaper AG, Ashby D, Delves HT, Clayton BE. The relationship between blood lead, blood pressure, stroke, and heart attacks in middle-aged British men. Environ Health Perspect 78:23–30 (1988).
42. Harlan WR. The relationship of blood lead levels to blood pressure in the U.S. population. Environ Health Perspect 78:9–13 (1988).
43. Schwartz J. The relationship between blood lead and blood pressure in the NHANES II survey. Environ Health Perspect 78:15–22 (1988).
44. Weiss ST, Munoz A, Stein A, Sparrow D, Speizer FE. The relationship of blood lead to systolic blood pressure in a longitudinal study of policemen. Environ Health Perspect 78:53–56 (1988).
45. ATSDR. Toxicological profile for lead. TP-92/12. Atlanta, GA:Agency for Toxic Substances and Disease Registry, 1993.